REMARKS

By an Office Action dated February 11, 2003 in the file of this application the Examiner rejected this application on a variety of grounds. Based on the changes to the claims made above, and the comments submitted herewith, reconsideration of the merits o this patent application is respectfully requested.

First the Examiner has persisted in the requirement for restriction. In order that the application be further prosecuted, the applicants have withdrawn the non-elected claims, without prejudice.

The Examiner objected to the specification because it contained a URL. The specification has been amended to remove that URL.

The Examiner also rejected the claims of this application under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner contends that the specification is not enabling for the limitation of the claims. The applicants respectfully traverse this requirement.

The applicants base their assertion as to the enablement of this application based on the shared genetic deficiencies of people with Tangier's disease and the single gene mutant WHAM chickens. Both humans with Tangier's disease and the WHAM chickens share a single mutation, in a single gene, for a single protein. Both those people and those chickens have a mutant form of the ABC1 protein which is inadequately functional. It has been previously known that WHAM chickens are incapable of proper cholesterol uptake in their intestines. This application, for the first time, points to the exact genetic reason for that deficiency, the function of the ABC1 gene and its resultant protein. It is true, as the Examiner suggests, that regulation of cholesterol transport from the diet is complex and does involve more receptors than ABC receptors and more ABC receptors than ABC1. However, it is equally clear that a deficiency in ABC1 activity results in reduced cholesterol uptake from the gut in both humans and chickens. The two data points of the humans with Tangier's disease and the WHAM chickens make this observation inescapable. While other mechanisms and routes may play a role, or have some importance in cholesterol uptake and regulation, the fact that the human condition known as Tangier's disease and the mutation in the WHAM chickens result from a mutation in the same protein is inescapable evidence that the activity of that protein is responsible for the unique physiological conditions shared the by the Tangier's patients and the WHAM chickens. That physiological condition includes reduced uptake of cholesterol from the intestines. This is compelling evidence that a reduction in ABC1 activity in the intestines will result in decreased absorption of cholesterol

from the intestines. The Examiner has provided no reason whatsoever to question whether this result would be obtained.

Note that this is all that Claim 1 requires. Claim 1 is a method for inhibiting cholesterol uptake in the gut. It is now known, without dispute, that ABC1 is responsible for, at least in part, cholesterol uptake in the gut. It is also known that there are demonstrated inhibitors of ABC1 activity, notably the sulfonylurea drugs. Since the activity desired is inhibition in the gut, and delivery to the gut may be obtained by oral ingestion, there is no lack of enablement related to delivery of the compound to the active site where inhibition is desired. The Examiner has provided no reason, other than a general sense of uncertainty in the world, why this would not occur. As such a rejection of these claims for lack of enablement is improper.

The second rejection was under §112, first paragraph, for written description. The Examiner asserts that the claims contain subject matter not described in the specification in such a way so as to reasonably convey to one of ordinary skill in the art that the applicants had possession of the claimed invention. The Examiner acknowledges that the specification teaches that sulfonylurea compounds inhibit ABC1 activity. The Examiner asserts that such a teaching is not sufficient for all sulfonylurea compounds. However, the specification here teaches other mechanisms to inhibit ABC1 activity. Note in the passage beginning in the specification at the bottom of page 6, and continuing on to page 7 where it is recited that one could construct an antisense genetic construct to lower expression of the ABC1 gene. The sequence of the gene is provided in the specification and the construction of antisense constructs to inhibit endogenous genes is a well known strategy to lower the activity of a protein in a subject. On page 8 of the specification is a description of the construction of antibodies to the ABC1 protein. The raising of antibodies to specific proteins or peptides is also well known to those of ordinary skill in the art. The external domains of the ABC1 protein are set forth on page 9 of the specification. These domains would allow the construction of antibodies which would target those regions as epitopes. This section of the specification is therefore clearly enabling for the production of antibodies specific to the extracellular regions of the ABC1 protein. This teaching is not acknowledged by the Examiner as well.

The applicants have enabled at least three different ways to lower the activity of the ABC1 protein *in vivo*. One involves a class of drugs in which at least one functional embodiment has been described, i.e., the sulfonylurea drugs. The applicants have enabled the construction of antisense constructs, which are well known as mechanisms to lower the

expression of proteins *in vivo*. Thirdly the applicants have identified methods to construct antibodies to the extracellular portions of the ABC1 protein, and even specified the portions of the protein against which such antibodies would be raised. Since again the critical target for the ABC1 inhibition effort is the gut, it is not a great difficulty to deliver the molecules in question or the effected site since all of these things may be safely orally ingested. Accordingly, the applicants have enabled several variations on how the lowering of ABC1 activity can be achieved. The claims are not overly broad, and do not encompass activity not enabled by the present specification.

It should be noted that it is not understood how this rejection is applied against the existing Claim 2 and the newly submitted Claim 22. The Examiner seems to acknowledge that the sulfonylurea compounds have activity as inhibitors of the ABC1 protein. It is believed, that, at a minimum, these claims should be free of this rejection.

The last rejection in the Office Action was under 35 U.S.C. §112, second paragraph, for indefiniteness. This claim was directed to Claim 5. The Examiner pointed out that Claim 3 and Claim 5 use the same words, and it was not clear how Claim 3 distinguished from Claim 5. The applicants have attempted to cure this difficulty by making it clear what Claim 3 was intended to cover. Note in the specification, again on the paragraph bridging pages 6 and 7, that one may lower the activity of the ABC1 protein either by directly targeting the protein and inhibiting the protein itself or by targeting the gene which expresses the protein to lower the level of total protein. The alternative strategies are to lower the efficiency of the ABC protein which is present or to simply lower the amount of the ABC protein which is present by targeting the gene which expresses it. Claim 5 was intended to recite by targeting the protein, as opposed to targeting the gene, which is recited in Claim 4. Language has been added to Claim 5 intended to make it clear that direct drug based inhibition of the ABC1 protein. The use of the word "drug" is contained in the specification on page 7. The word "direct" has been added by the applicants to distinguish action on the molecule itself from activity on the gene which expresses the protein. It is believed that this addition of one word is not new matter in the specification of this application, given the context of the description on page 7 of the specification.

Wherefore the Examiner is respectfully requested to revisit the merits of this patent application. An early and favorable reply is solicited.

A separate petition for extension of time for three months is submitted herewith so that this response will be considered as timely filed. Please charge the fee to Deposit Account No. 17-0055.

Respectfully submitted,

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